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10/584,345	02/26/2007	Nobuaki Takahashi	081356-0262	3671

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,345	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/06/2010, 01/20/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *137-139* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *137-139* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/06/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 01/06/2010, has been entered.
Claims 138-139 have been amended.

Claims 1-136 have been canceled previously.

Claims 137-139 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's amendment, filed 01/06/2010.

The rejections of record can be found in previous Office Action, mailed 10/06/2009.

3. Applicant's Information Disclosure Statement, filed 06/23/2006, providing each cited foreign patent document and each non-patent literature publication cited therein has been considered and a signed copy is provided with this Office Action.

4. Upon reconsideration of applicant's arguments directing written support for the instant claims, filed 01/06/2010,;
The previous rejection under 35 U.S.C. § 112, first paragraph, written description has been withdrawn.

5. Rebuttal to Applicant's arguments, filed 01/02/2010, in conjunction with the signed Takahashi Declaration under 37 CFR 1.132, filed 01/20/2010 with respect to the Obviousness Rejections of record and reiterated herein.

Applicant's arguments, filed 01/02/2010, in conjunction with the signed Takahashi Declaration under 37 CFR 1.132, filed 01/20/2010, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant argues the following.

Without acquiescing to this perspective on the prior art, Applicants submit that the claimed antibody displays activity, both in vitro and in vivo, that would have been wholly unexpected in the art, thus vindicating the patentability of the present claims. Elaborating on this point below, Applicants also make of record the accompanying "Declaration under 3 7 C.F.R. § 1.13 2 by Dr. Nobuaki Takahashi" ("Takahashi Declaration"). Dr. Takahashi is a named co-inventor on this application. Applicants were unable to obtain Dr. Takahashi's signature of the declaration prior to filing of the present reply. However, Applicants will submit an executed version of the Takahashi Declaration shortly.

As noted above, the antibody of the claimed invention is designated "4D11G4PE" in Applicants' specification, e.g., on page 35, line 7 from the bottom, and is a mutant of an anti-CD40 antagonistic antibody, designated "4D11," which is described in Mikayama PCT and Mikayama. See the specification, e.g., in the initial two paragraphs on page 5, and also the Takahashi Declaration at ¶ 5.

The 4D11G4PE antibody is an antagonistic anti-CD40 antibody, containing the variable regions of the 4D 11 antibody and the constant region of the human IgG4 subclass of antibodies. Relative to 4D11, moreover, the antibody of Applicants' invention contains two amino-acid substitutions in the constant region of the heavy chain.

More specifically, the 4D11G4PE antibody contains two amino acid substitutions at positions $228P and L235E, as indicated by the EU index of Kabat et al., a standard antibody notation system. "S228P" and "L235E" indicate that the serine amino acid at Kabat position 228 was substituted for the amino acid proline and that the leucine amino acid at Kabat position 235 was substituted for the amino acid glutamic acid. The mature heavy and light chains of the 4D 11G4PE antibody in the captioned application correspond to amino acids 27 to 474 of SEQ ID NO: 140 and amino acids 23 to 235 of SEQ ID NO: 142, respectively. See Takahashi Declaration at ¶ 7.

By way of some background, CD40 is an antigen that is expressed on B cells and dendritic cells. CD40 interacts with a ligand, CD40L, which is expressed on CD4+T cells. Dendritic cells are activated when CD40 expressed on dendritic cells interacts with CD40L on CD4+T cells. The activation of dendritic cells enhances the expression of auxiliary stimulants, such as CD80 and CD86, and the production of 1L-12, which results in induction of cellular immunity by cytotoxic T lymphocytes. Furthermore, when CD40 on B cells interacts with CD40L on CD4+ T cells, B cells grow and differentiate, and antibody production by the B cells is enhanced, resulting in induction of humoral immunity. An antagonistic anti-CD40 antibody binds to CD40 on B cells and dendritic cells, respectively, to block the interaction between CD40 and CD40L on CD4+ T cells, which in turn inhibits the induction of cellular immunity and humoral immunity. Such an antibody is expected to be useful as a suppressor of rejection, following organ transplantation, or as a drug for treating autoimmune disease. See Takahashi Declaration at ¶ 9.

Yet, when an antibody that recognizes antigens on cells involved in immune responses, such as B cells and dendritic cells, binds to an antigen on such cells, then the Fc region of the antibody interacts with Fc receptors presented by other cells, which induces signals for an immune response in some cases. See Takahashi Declaration at ¶ 10.

Therefore, when an antibody such as an antagonistic anti-CD40 antibody is used to suppress rejection after organ transplantation or to treat autoimmune disease, "it is important that anti-CD40 antagonistic antibodies have no activity to induce signals by their in vivo crosslinking via Fc receptors, even if the ADCC activity cannot be detected." Specification at page 27, last full sentence (emphasis added). This is so because, if such antibodies "induce an agonistic activity due to some effect after they are administered to patients, however weak [the activity] may be, [then] the symptoms may worsen in contrast to the desired therapeutic effect." Id. at page 28, second full sentence (emphasis and bracketing added). See also the Takahashi Declaration at ¶ 10.

Accordingly, for an antagonistic anti-CD40 antibody it is very important to avoid the induction of CD40 signals (i. e., agonistic activity) brought about by the crosslinking of the antibody via Fc receptors in vivo. See Takahashi Declaration at ¶ 11. The claimed antibody, 4D11G4PE, does not exhibit agonistic activity in vitro or in vivo. Thus, Example 15 and Figure 16 of the captioned application demonstrate that 4D 11G4PE does not enhance production of IL-12, an indicator of agonistic activity in vivo. See the Takahashi Declaration at ¶ 12.

This lack of agonistic activity in vivo is critical to the use of an anti-CD40 antibody in the prevention of transplant rejection or as a therapy for autoimmune disease. Id. Erickson-Miller, Taylor, and Holmes describe antibodies that recognize targets other than CD40 but that contain the S228P and L235E mutations in the heavy chain constant region. These three references state that the S228P and L235E mutations result in reduced effector function, but none even hints at how the mutations of the heavy chain constant region might effect in vivo agonistic activity by virtue of the described crosslinking of the antibody to an Fc receptor. See Erickson-Miller at col. 11, 11. 48-52, Taylor at col. 6, 11. 60-66, and Holmes at col. 10, 11.66 - col. 11, 11. 5.

With no basis for expecting that the same mutations would not have agonistic activity in vivo due to such crosslinking, the skilled artisan could not have predicted that an anti-CD40 antibody with these mutations would lack agonistic activity in vivo. As Dr. Takahashi attests, ... a knowledgeable person, informed by the disclosures of Erickson-Miller, Holmes and Taylor, could not have reasonably predicted whether combining the human IgG4 constant region, with the S228P and L235E mutations and the variable region from the 4D11 antibody would yield an anti-CD40 antibody that exhibited antagonistic activity in vitro and, more importantly, in vivo. Takahashi Declaration at ¶ 17.

In this regard Dr. Takahashi discusses a study by Reddy et al., J. Immunology 164:1925-33 (2000), of an anti-CD4 antibody, "clenoliximab," which has the same S228P and L235E mutations as the antibody of Applicants' claimed invention. As Dr. Takahashi explains, Reddy et al. documented that clenoliximab loses the binding activity to Fc receptor in vitro (Figure 4B). Clenoliximab induces strong CD4 modulation in vivo, however, due to the crosslinking of the antibody on CD4 via Fc receptors. Takahashi Declaration at ¶ 18.

With respect to Fc receptor activation, therefore, an antibody disclosed in the art that has the same S228P and L235E mutations as the inventive antibody displays divergent in vivo properties. This illustrates that the in vitro properties of an antibody, with respect to Fc receptor activation, is not predictive of activity in vivo. By the same token, the skilled artisan could not and would not have generalized from the reports of in vitro activity by Erickson-Miller, Holmes, and Taylor to an a priori expectation that another antibody with the S228P and L235E mutations, as presently claimed, would display a like activity in vivo.

To the contrary, Reddy et al. shows and the Takahashi Declaration attests that an ability by a putative therapeutic antibody not to activate the immune response via Fc cross-linking in vivo is wholly unpredictable. Yet, as shown in Example 15 and Figure 16 of the specification, the 4D 11G4PE antibody does not enhance IL-12 production, an indicator of agonistic activity in vivo which likewise is unpredictable, and also delays skin graft rejection (Example 19).

In summary, one of ordinary skill could not have predicted, based on the cited references, that the 4D 11G4PE antibody would have the documented activity both in vitro and in vivo. The evidence of record on point, including the Takahashi Declaration, therefore warrants withdrawal of the pending obviousness rejection.

In contrast to applicant's / Takahashi's assertions, the teachings of the primary and secondary references are consistent with the applicant's Takahashi's assertions with respect to modifying antibodies, including the claimed anti-CD40 antibodies to decrease the immunogenicity and the binding to Fc receptors for the same reasons as applicant's/Takahashi's assertions.

For example, see the following excerpts.

Specifically, there may be a risk that the antibodies would become agonistic antibodies. Even if the antigenicity is low, anti-CD40 antibodies may be cross-linked with antibody receptors (FcR). From these points, a preferred antagonistic antibody is a human antibody, which binds specifically to CD40, suppresses the binding of CD40L, and does not activate CD40 even by cross-linking, and exhibits weak binding to FcR.

See paragraph [0011] on page 4 of EP 1391464.

See columns 6-7, overlapping paragraph of U.S. Patent No. 7,193,064.

3) The antibody of the present invention can be altered to an antibody of a different subclass (for example, see EP314161 publication), by modification by genetic engineering techniques known by a person skilled in the art, specifically by substituting a region that defines the subclass of an antibody heavy chain with a region that defines another subclass. A heavy chain variable region and the constant region of another subclass can be directly linked. For example, an alteration of the subclass of the antibody of the present invention to IgG2 or IgG4 makes it possible to lower the binding degree of the antibody to a Fc receptor. Specifically, NheI site (GCTAGC) is introduced into a human antibody heavy chain, EU index 118 (Ala), 119 (Ser) site according to Kabat et al (Sequence of Proteins of Immunological Interest, 5.sup.th Ed. Public Health Service, National Institute of Health, Bethesda, Md. (1991)). By digestion using the restriction enzyme, switching to another subclass, IgG, can be performed without altering the amino acid. Moreover, artificial alteration of the amino acid sequence of a constant region, or the binding of a constant region sequence having such an altered sequence with the variable region of the antibody of the present invention can lower the binding degree to a Fc receptor (Lund J., et al., J. Immunol. 1991 vol 147: 2657-2662), or can also increase or decrease CDC activity (Tao M., et al., J. Exp. Med. 1991 vol 1025 1028, Idusogie E E., et al., J. Immunol. 2001 vol 166: 2571 5). Furthermore, to avoid the action of ADCC, CDC or the like, only IgG2 or IgG4 subclass antibodies can be previously selected. In addition, the binding of a radionuclide, bacterial toxin, chemotherapeutant, prodrug or the like with the antibody of the present invention can further enhance the therapeutic effect against disease such as cancer.

See paragraph [0039] on page 4 of EP 1391464.

See column 15, paragraph 3 of U.S. patent No. 7,193,064.

Also, see In the Case of Antagonistic Antibody on pages 10-11 of EP 1391464 and in columns 14-17 of U.S. Patent No. 7,193,064.

Again, the secondary references are all consistent with modifying IgG4 subclass with the S228P and L235E (PE mutation) for the very same reason as the primary references as well as applicant's/Takahashi's assertions as follows.

Erickson-Miller et al. (see entire document, particularly column 11, paragraph 4) teach the following.

Preferably, the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. IgG1, k and IgG4, k are preferred. Particularly preferred is IgG 4, k. Most particularly preferred is the IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function. This IgG4 subtype variant is known herein as IgG4PE. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Holmes et al. (see entire document, particularly column 11, paragraph 4) teach the following.

Preferably, the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. IgG1, k and IgG4, k are preferred. Particularly preferred is IgG 4, k. Most particularly preferred is the IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function. This IgG4 subtype variant is known herein as IgG4PE. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Taylor (see entire document, particularly teach the following.

The engineered V regions are then joined to one or more different human or Old World ape constant regions depending on the desired secondary immune functions such as complement fixation or Fc receptor binding. Human constant regions can be selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. An IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function can also be selected. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Applicant / Takahashi assert that the observations concerning the strong CD4 receptor modulation in vivo due to crosslinking of the antibody on CD4 via Fc receptors described by Reddy et al. (J. Immunol. 164: 1925-1933, 200) (1449; #F8), wherein such activity must be avoided for an antagonistic anti-CD40 antibody.

Reddy et al. note various possible explanations for such observations, including the role or presence of rheumatoid factor and note that various factors can potentially influence the in vitro and in vivo properties of antibodies to cell surface molecules, including the nature of the targeted molecule, its cellular and tissue distribution and the antigen density on the cell surface (see page 1932 and Abstract of Reddy et al.).

In response to applicant's assertions based upon the recombinant anti-CD4 antibody clenoliximab and consistent with remarks in Reddy et al.,

Sharma et al. (Pharmacol Expo Ther 293: 33-41, 2000) also note various indirect response mechanisms that are associated with keliximab and clenoliximab as well as the dose response nature of the immomodulatory effects, including the differences in the concnetrationsacheived in vivo and those used in the in vitro studies (See entire document, including Discussion / Pharmacodynamics).

While there may be differences between CD4 and CD40 or their cell surface receptors or between specific antibodies (e.g., one anti-CD4 or anti-CD40 antibody from another anti-CD4 or anti-CD40 antibody) as well as differences in assays and assay conditions,

the Office is not equipped to manufacture the claimed product and/or prior art products.

It is noteworthy that both clenoliximab and keliximab anti-CD4 antibodies maintain immunomodulatory effects, which was the key design feature of said antibodies.

Again, the IgG4 PE modifications taught by the prior art are consistent with the very same advantages of the goals the PE modifications as well as the possible disadvantages not making such modifications as the claimed invention.

Obviousness does not require absolute predictability of success … all that is required is a reasonable expectation of success.". O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988)

An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art. See In re Kubin, 90 USPQ2d 1417 (Fed. Cir. 2009).

Also, see the analysis of the KSR rationales in the obviousness rejections of record and reiterated herein. Also, see KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (2007).

One of ordinary skill in the art at the time the invention was made would have been motivated to provide modified IgG4 immunoglobulin variants of the 4D11 anti-CD40 antibody, given the teachings of the prior art of providing IgG4 modifications to therapeutic antibodies of interest in order to increase half-life or to modify effector function of therapeutic antibodies, as taught by the secondary references. A person of ordinary skill in the art at the time the invention was made would have been motivated by taking the advantages of the providing such IgG4 modifications to therapeutic antibodies of interest with an expectation of success, since such properties and advantages are consistent with human therapeutic regimens associated with treating said conditions at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

See the rejections below for a more complete anlysis of the prior art rejection.

Applicant's arguments have not been found persuasive.

6. Claims 137-139 stand rejected under 35 U.S.C. § 103(a) as being unpatentable Mikayama et al. (WO 02/088186) (1449; filed 06/23/2006) as evidenced by Mikayama et al. EP 1391464 A1) (1449; #C5) in view of Erickson-Miller et al. (U.S. Patent No. 6,998,124), Taylor (U.S. Patent No. 6,936,698) and Holmes et al. (U.S. Patent No. 6,376,653) for the reasons of record .

Applicant's arguments, filed 01/02/2010, in conjunction with the signed Takahashi Declaration under 37 CFR 1.132, filed 01/20/2010, have been fully considered but have not been found convincing essentially for the reasons of record and that addressed above in Section. 5.

The following is reiterated for applicant's convenience.

Mikayama et al. (WO 02/088186) teach the 4D11 anti-CD40 antibody (e.g., see section (12) and Table on page 11; pages 23, 27, 28, 29, 38, 42, 51-53, and Claims)) as well as pharmaceutical compositions thereof as well as prophylactic and therapeutic methods to inhibit immunological graft rejection of GVHD (e.g., see Pharmaceutical Compositions on columns 15-17) (see entire document).

Given that Mikayama et al. (WO 02/088186) is in Japanese,
Mikayama et al. (EP 1391464 A1) is provided as evidence of the English equivalent Mikayama et al. (WO 02/088186) in view of Erickson-Miller et al. (U.S. Patent No. 6,998,124), Taylor (U.S. Patent No. 6,936,698) and Holmes et al. (U.S. Patent No. 6,376,653).

Mikayama et al. (EP 1391464 A1) teach the 4D11 anti-CD40 antibody (see pages 6, , 7, 10, 11, 14, 15, 16, 20, 21, 24, 34, 35; Brief Description of the Drawings on page 12; Claims)
as well as pharmaceutical compositions thereof as well as prophylactic and therapeutic methods to inhibit immunological graft rejection of GVHD (e.g., see Pharmaceutical Compositions on pages 11-12)

Mikayama et al. differs from the claimed invention by not explicitly teachings of modifying the base/reference 4D11 antibody of the claimed invention.

The following references provide for modifying therapeutic antibodies containing point mutations S228P and L235E in the IgG4 constant region at the time the invention was made.

Erickson-Miller et al. (see entire document, particularly column 11, paragraph 4) teach the following.
Preferably, the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. IgG1, k and IgG4, k are preferred. Particularly preferred is IgG 4, k. Most particularly preferred is the IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function. This IgG4 subtype variant is known herein as IgG4PE. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Holmes et al. (see entire document, particularly column 11, paragraph 4) teach the following.
Preferably, the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. IgG1, k and IgG4, k are preferred. Particularly preferred is IgG 4, k. Most particularly preferred is the IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function. This IgG4 subtype variant is known herein as IgG4PE. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Taylor (see entire document, particularly teach the following.
The engineered V regions are then joined to one or more different human or Old World ape constant regions depending on the desired secondary immune functions such as complement fixation or Fc receptor binding. Human constant regions can be selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. An IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function can also be selected. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

One of ordinary skill in the art at the time the invention was made would have been motivated to provide modified IgG4 immunoglobulin variants of the 4D11 anti-CD40 antibody, given the teachings of the prior art of providing IgG4 modifications to therapeutic antibodies of interest in order to increase half-life or to modify effector function of therapeutic antibodies, as taught by the secondary references. A person of ordinary skill in the art at the time the invention was made would have been motivated by taking the advantages of the providing such IgG4 modifications to therapeutic antibodies of interest with an expectation of success, since such properties and advantages are consistent with human therapeutic regimens associated with treating said conditions at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (e.g., 4D11 antagonistic anti-CD40 antibody and known modifications to IgG4-based therapeutic antibodies to modify effector function and/or increase half-life) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (modifying therapeutic antibodies of interest) to target cells of interest in order to treat diseases of interest (e.g., antagonistic 4D11 antibodies and inhibiting graft rejection) with no change in their respective functions and the combination would have yielded nothing more than predictable results of providing therapeutic 4D11 antagonistic antibodies as well as their applicability in the inhibition of graft rejection.

The rationale to support a conclusion that the claims would have been obvious is that a method of decreasing effector function and/or increasing half-life via modifying IgG4-based therapeutic antibodies of interest was made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known recombinant methods of modifying IgG4-based therapeutic antibodies in order to increase the half-life and/or to modify effector function of therapeutic antibodies of interest to target cells and molecules of interest in various modalities, including the inhibition of graft rejection and would have been predictable to one of ordinary skill in the art at the time the invention was made.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (modifying IgG4-based therapeutic antibodies in order to increase half-life and/or to modify effector function) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying these known techniques to a known product (e.g., 4D11 anti-CD40 antibodies) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g., modifying IgG4 therapeutic antibodies of interest to increase half-life and/or modify effector function) within his or her technical grasp. This leads to the anticipated success of modifying therapeutic antibodies such as the 4D11 anti-CD40 antibodies with increase half-life and/or modified effector function. It is likely the product not of innovation but of ordinary skill and common sense.

Since modifying IgG4-based therapeutic antibodies of interest would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of a modified IgG4-based 4D11 antibody to increase half-life and/or to modify effector function. The prior art had recognized the advantages of modifying therapeutic antibodies to comprise modified IgG4-based antibodies to increase half-life and/or to modify effector function and had suggested and relied upon such modifications to accomplish this goal. The claims were obvious because it would have been obvious to try modifying the known 4D11 antibody as a modified IgG4-based antibody to increase half-life and/or to modify effector function with a reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to employ 4D11 antibodies as therapeutic agents,
incorporating known IgG4-based modifications to therapeutic antibodies of interest to increase half-life and/or to modify effector function in the 4D11 anti-CD40 antibody would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic molecules with improved half-life and desirable functions.

Applicant's arguments have not been found persuasive.

7. Claims 137-139 are rejected under 35 U.S.C. § 103(a) as being unpatentable Mikayama et al. (U.S. Patent No. 7,193,064 (1449; #E1) in view of Erickson-Miller et al. (U.S. Patent No. 6,998,124), Taylor (U.S. Patent No. 6,936,698) and Holmes et al. (U.S. Patent No. 6,376,653) for the reasons of record .

Applicant's arguments, filed 01/02/2010, in conjunction with the signed Takahashi Declaration under 37 CFR 1.132, filed 01/20/2010, have been fully considered but have not been found convincing essentially for the reasons of record and that addressed above in Section 5.

The following is reiterated for applicant's convenience.

Mikayama et al. teach the 4D11 anti-CD40 antibody (e.g., see Section (12) on column 8; Table on column 9; Sections (13)-(14) on column 9; Section (j) on column 15; Examples 2-4 on columns 18-22; Example 14 on columns 28-29; Example 17, particularly columns 43-44; Example 19 on columns 55-56; Figures 15 and 18 and 19, see Brief Description of the Drawings on column 17; and Claims) as well as pharmaceutical compositions thereof as well as prophylactic and therapeutic methods to inhibit immunological graft rejection of GVHD (e.g., see Pharmaceutical Compositions on columns 15-17)

Mikayama et al. differs from the claimed invention by not explicitly teachings of modifying the base/reference 4D11 antibody of the claimed invention, particularly as it read on the antibodies containing point mutations S228P and L235E in the IgG4 constant region (e.g., see Modification of Antagonistic Antibodies on pages Example 11 of the instant application)

The following references provide for modifying therapeutic antibodies containing point mutations S228P and L235E in the IgG4 constant region at the time the invention was made.

Erickson-Miller et al. (see entire document, particularly column 11, paragraph 4) teach the following.
Preferably, the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. IgG1, k and IgG4, k are preferred. Particularly preferred is IgG 4, k. Most particularly preferred is the IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function. This IgG4 subtype variant is known herein as IgG4PE. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Holmes et al. (see entire document, particularly column 11, paragraph 4) teach the following.
Preferably, the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. IgG1, k and IgG4, k are preferred. Particularly preferred is IgG 4, k. Most particularly preferred is the IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function. This IgG4 subtype variant is known herein as IgG4PE. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

Taylor (see entire document, particularly teach the following.
The engineered V regions are then joined to one or more different human or Old World ape constant regions depending on the desired secondary immune functions such as complement fixation or Fc receptor binding. Human constant regions can be selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. An IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function can also be selected. See U.S. Pat. Nos. 5,624,821 and 5,648,260.

One of ordinary skill in the art at the time the invention was made would have been motivated to provide modified IgG4 immunoglobulin variants of the 4D11 anti-CD40 antibody, given the teachings of the prior art of providing IgG4 modifications to therapeutic antibodies of interest in order to increase half-life or to modify effector function of therapeutic antibodies, as taught by the secondary references. A person of ordinary skill in the art at the time the invention was made would have been motivated by taking the advantages of the providing such IgG4 modifications to therapeutic antibodies of interest with an expectation of success, since such properties and advantages are consistent with human therapeutic regimens associated with treating said conditions at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (e.g., 4D11 antagonistic anti-CD40 antibody and known modifications to IgG4-based therapeutic antibodies to modify effector function and/or increase half-life) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (modifying therapeutic antibodies of interest) to target cells of interest in order to treat diseases of interest (e.g., antagonistic 4D11 antibodies and inhibiting graft rejection) with no change in their respective functions and the combination would have yielded nothing more than predictable results of providing therapeutic 4D11 antagonistic antibodies as well as their applicability in the inhibition of graft rejection.

The rationale to support a conclusion that the claims would have been obvious is that a method of decreasing effector function and/or increasing half-life via modifying IgG4-based therapeutic antibodies of interest was made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known recombinant methods of modifying IgG4-based therapeutic antibodies in order to increase the half-life and/or to modify effector function of therapeutic antibodies of interest to target cells and molecules of interest in various modalities, including the inhibition of graft rejection and would have been predictable to one of ordinary skill in the art at the time the invention was made.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (modifying IgG4-based therapeutic antibodies in order to increase half-life and/or to modify effector function) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying these known techniques to a known product (e.g., 4D11 anti-CD40 antibodies) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g., modifying IgG4 therapeutic antibodies of interest to increase half-life and/or modify effector function) within his or her technical grasp. This leads to the anticipated success of modifying therapeutic antibodies such as the 4D11 anti-CD40 antibodies with increase half-life and/or modified effector function. It is likely the product not of innovation but of ordinary skill and common sense.

Since modifying IgG4-based therapeutic antibodies of interest would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of a modified IgG4-based 4D11 antibody to increase half-life and/or to modify effector function. The prior art had recognized the advantages of modifying therapeutic antibodies to comprise modified IgG4-based antibodies to increase half-life and/or to modify effector function and had suggested and relied upon such modifications to accomplish this goal. The claims were obvious because it would have been obvious to try modifying the known 4D11 antibody as a modified IgG4-based antibody to increase half-life and/or to modify effector function with a reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to employ 4D11 antibodies as therapeutic agents,
incorporating known IgG4-based modifications to therapeutic antibodies of interest to increase half-life and/or to modify effector function in the 4D11 anti-CD40 antibody would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing therapeutic molecules with improved half-life and desirable functions.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to provide antagonistic anti-PSGL-1 antibodies to treat a variety of inflammatory, autoimmune and cancer conditions,
incorporating multimeric antagonistic anti-PSGL-1 antibodies in kits comprising said antibodies and instructions for use would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such kits for convenience, economy and the expected benefit of optimizing standardization of preparing and using therapeutic antibodies of interest at the time the invention was made.

Applicant's arguments have not been found persuasive.

8. Claims 137-139 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of USSN 11/663,340.

Although the claims are not identical, the claims appear to be drawn to the same or nearly the same CD40-specific antibodies, comprising the same or nearly the same IgG4 modifications. In addition, the copending claims include compositions for the intended use of in the treatment of transplantation. The claims anticipate or render obvious one another.

Applicants respectfully request, therefore, that the ODP rejection be held in abeyance until the remaining rejections are overcome.

The rejection is maintained for the reasons of record.

9. Upon reconsideration of applicant's remarks concerning the filing dates of commonly assigned USSN 11/663,340, the previous request concerning common ownership at the time the invention was made has been withdrawn

10. No claim allowed.

11. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
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